A. Regarding the Amendments

The specification has been amended at the first line to remove "X" from the first sentence, thereby stating "This application is a continuation of application U.S. Serial No. 08/526,708 filed September 11, 1995." This amendment does not add new matter.

New claim 13 is directed to a conjugate containing a peptide that selectively homes to brain linked to a moiety that is a toxin, drug, chemotherapeutic agent, cell or liposome. New claim 21 is directed to a conjugate containing a X_1SRLX_2 (SEQ ID NO: 45) peptide that selectively homes to brain linked to a moiety that is a toxin, drug, chemotherapeutic agent, cell or liposome. New claim 25 is directed to a conjugate containing a X_3VLRX_4 (SEQ ID NO:46) peptide that selectively homes to brain linked to a moiety that is a toxin, drug, chemotherapeutic agent, cell or liposome. Support for new claims 13, 21 and 25 is found in the specification, for example, at page 24, line 25, to page 25, line 2, which indicates that a brain homing peptide can be linked to a moiety and that the moiety can be, for example, a toxin or drug such as a chemotherapeutic agent. Additional support for new claims 13, 21 and 25 can be found in the specification, for example, at page 25, lines 3-16, which indicates that an organ homing peptide of the invention can be linked to a moiety that is a cell, such as a red blood cell, a white blood cell or cytotoxic cell, and in the specification, for example, at page 27, lines 8-18, which indicates that organ homing molecules can be linked to liposomes. Further support for

new claims 21 and 25 is found in original claims 2 and 5, respectively, and in the specification, for example, at page 29, lines 3-7, which discloses brain homing peptides containing the SRL and VLR motifs.

New claim 14, directed to a peptide that selectively homes to brain and has the sequence X_1SRLX_2 (SEQ ID NO:45), where X_1 and X_2 each is 1 to 10 independently selected amino acids, also has been added. New claim 14 supported by original claim 2 and in the specification, for example, at page 29, lines 3-7, which discloses brain homing peptides containing the SRL motif.

New claims 15, 17 and 19 are directed to X_1SRLX_2 peptides that further include the sequence CLSSRLDAC (SEQ ID NO:3), CNSRLHLRC (SEQ ID NO: 1) or CNSRLQLRC (SEQ ID NO: 5), respectively. These new claims are supported by original claims 3 and 4 and in the specification, for example, at page 34, lines 10-18, and in Table 1, which indicate that phage containing peptides with SEQ ID NOs:1, 3 and 5 selectively home to brain. New claims 16, 18 and 20 are directed to peptides CLSSRLDAC (SEQ ID NO:3), CNSRLHLRC (SEQ ID NO: 1) and CNSRLQLRC (SEQ ID NO: 5), respectively. Support for these new claims can be found in original claims 3 and 4 and the specification, for example, at Table 1, which discloses the peptides SEQ ID NO:1, 3 and 5.

New claim 22 is directed to a conjugate containing a peptide that selectively homes to brain linked to a moiety, where the moiety is a toxin, drug, chemotherapeutic agent, cell or liposome, and where the peptide includes the sequence CNSRLHLRC (SEQ ID NO: 1), CLSSRLDAC (SEQ ID NO: 3) and CNSRLQLRC (SEQ ID

NO: 5). New claim 23 is directed to a conjugate containing the brain homing peptide CNSRLHLRC (SEQ ID NO: 1), CLSSRLDAC (SEQ ID NO: 3) and CNSRLQLRC (SEQ ID NO: 5) linked to a moiety that is a toxin, drug, chemotherapeutic agent, cell or liposome. New claims 22 and 23 are supported by original claims 3 and 4 and in the specification as discussed above in regard to claim 21. New claims 22 and 23 also are supported in the specification, for example, at page 34, lines 13-18, and Table 1, which indicate that phage containing peptides with SEQ ID NO:1, 3 and 5 selectively home to brain.

New claim 24 is directed to a cyclic peptide that selectively homes to brain and has the amino acid sequence X_3VLRX_4 (SEQ ID NO: 46), where X_3 is absent or is 1 to 10 independently selected amino acids and X_4 is 1 to 20 independently selected amino acids. New claim 24 is supported by original claim 5 and in the specification, for example, at page 31, lines 6-13, which discloses that peptide libraries to be screened by in vivo panning can display cyclic peptides. New claim 24 further is supported in the specification, for example, at page 29, lines 3-7, which discloses brain homing peptides containing the VLR motif.

New claim 26 is directed to a conjugate containing a peptide that selectively homes to brain linked to a moiety, where the moiety is a toxin, drug, chemotherapeutic agent, cell or liposome, and where the peptide includes the sequence CVLRGGRC (SEQ ID NO: 4) or WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16). New claim 27 is directed to a conjugate containing the brain homing peptide CVLRGGRC (SEQ ID NO: 4) or WRCVLREGPAGGCAWFNRHRL (SEQ ID

NO: 16) linked to a moiety that is a toxin, drug, chemotherapeutic agent, cell or liposome. New claims 26 and 27 are supported by original claim 6 and in the specification as discussed above in regard to claim 25. New claims 26 and 27 also are supported in the specification, for example, at page 34, lines 13-18, and Table 1, which indicate that phage containing peptides with SEQ ID NO:4 and 16 selectively home to brain.

New claims 28, 30, 32, 34, 36, 38 and 40 are directed to peptides that selectively home to brain which include the sequence CVLRGGRC (SEQ ID NO: 4), WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16), CENWWGDVC (SEQ ID NO: 2) CGVRLGC (SEQ ID NO: 6), CKDWGRIC (SEQ ID NO: 7), CLDWGRIC (SEQ ID NO: 8) or CTRITESC (SEQ ID NO: 9), respectively. Similarly, new claims 29, 31, 33, 35, 37, 39 and 41 are directed to peptides that selectively home to brain and consist of the sequence CVLRGGRC (SEQ ID NO: 4), WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16), CENWWGDVC (SEQ ID NO: 2) CGVRLGC (SEQ ID NO: 6), CKDWGRIC (SEQ ID NO: 7), CLDWGRIC (SEQ ID NO: 8) and CTRITESC (SEQ ID NO: 9), respectively. Support for new claims 28 to 41 is found in the specification, for example, at page 34, lines 14-23, and Table 1, which indicate that phage containing peptides with SEQ ID NO:2, 4, 6, 7, 8, 9 and 16 selectively home to brain.

Similarly, new claims 29, 31, 33, 35, 37, 39 and 41 are directed to peptides that selectively home to brain and consist of the sequence CVLRGGRC (SEQ ID NO: 4), WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16), CENWWGDVC (SEQ ID NO: 2) CGVRLGC (SEQ ID NO: 6), CKDWGRIC (SEQ ID NO: 7), CLDWGRIC (SEQ ID NO: 8) or CTRITESC (SEQ ID NO: 9), respectively. Support for these new claims is found

in the specification, for example, at Table 1, which discloses the peptides SEQ ID NO:2, 4, 6, 7, 8, 9 and 16.

B. Regarding the Rejections

Regarding the rejection under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 2 and 5 under 35 U.S.C. § 112, first paragraph, respectfully is traversed. The Office Action indicates that the specification fails to enable the full scope of the claims drawn to brain homing peptides having the amino acid sequence X_1SRLX_2 and X_3VLRX_4 and alleges that only peptide CLSSRLDAC (SEQ ID NO:3) is enabled. In particular, the Office Action indicates that brain homing, defined in the specification as at least 2-fold greater specific binding to brain than to a control organ, is not reported in the specification, except for CLSSRLDAC (SEQ ID NO:3), and further indicates that competition experiments such as the synthetic peptide competition experiments disclosed in Examples II.C. or II.D. would have been required to be assured of the brain homing properties of a peptide. The Office Action concludes that such competition experiments constitute undue experimentation. In view of the cancellation of claims 2 and 5, Applicants will address this ground for rejection as it applies to new claims 14, 21, 24 and 25.

Applicants submit that the specification enables a variety of peptides that selectively home to brain, including but

not limited to peptide CLSSRLDAC (SEQ ID NO: 3). In regard to selective homing, the specification teaches that a molecule that "selectively homes" to an organ binds relatively specifically to a target molecule present in one or a few selected organs and generally is characterized by at least a 2-fold greater specific binding of the molecule to the selected organ as compared to a control organ (page 15, lines 3-17). Applicants also direct the Examiner's attention to the specification at page 37, lines 1-4, which indicates that a variety of peptides demonstrated at least 2-fold greater specific binding to brain as compared to kidney. Specifically, the ratio of selective homing to brain relative to kidney for peptides CNSRLHLRC (SEQ ID NO: 1), CLSSRLDAC (SEQ ID NO: 3), CENWWGDVC (SEQ ID NO: 2) and WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16) was 8-fold, 8-fold, 4-fold and 9-fold, respectively. Thus, the specification discloses a variety of peptides that "selectively home" to brain, as demonstrated by at least 2-fold greater specific binding to brain as compared to kidney and in agreement with the definition of an organ homing molecule at page 15, lines 3-17.

Applicants further assert that demonstration of at least 2-fold greater specific binding is sufficient to establish that a peptide of the invention homes to brain without additional laboratory analysis. The Office Action indicates that, due to the highly unpredictable nature of the art, competition experiments would have been required to establish that a peptide selectively homes to brain and further asserts that such competition experiments constitute undue experimentation. Unpredictability of the art is allegedly demonstrated by the fact that phage expressing CLSSRLDAC (SEQ ID NO: 3) and

WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16) were inhibited from homing to brain by synthetic peptide CLSSRLDAC (SEQ ID NO: 3), while homing of phage expressing CENWWGDVC (SEQ ID NO: 2) was not affected by competition with the same synthetic peptide (see Example II.C.; page 39, lines 18-32). Applicants submit that, in spite of the lack of competition of CENWWGDVC (SEQ ID NO: 2) by CLSSRLDAC (SEQ ID NO: 3), CENWWGDVC (SEQ ID NO: 2) is a brain homing peptide of the invention; the lack of competition merely indicates that CENWWGDVC (SEQ ID NO: 2) specifically homes to brain by binding a different target molecule than the molecule recognized by CLSSRLDAC (SEQ ID NO: 3). See, for example, the specification at page 39, lines 28-32, which indicates that SEQ ID NO: 2 recognizes a different brain target molecule than SEQ ID NO: 3. Thus, the competition experiments disclosed in the subject application confirm the selective brain homing properties of peptides CLSSRLDAC (SEQ ID NO: 3), CENWWGDVC (SEQ ID NO: 2) and WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16) and do not support unpredictability in the art. In view of the teachings in the specification, Applicants submit that demonstration of at least 2-fold greater specific binding to brain as compared to a control organ is sufficient to establish that a peptide of the invention selectively homes to brain.

In summary, given that a variety of peptides are disclosed in the specification as having the ability to selectively home to brain, Applicants submit that the specification enables the full scope of claims 14, 21, 24 and 25. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be removed.

Regarding the rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 2 and 5 under 35 U.S.C. § 112, first paragraph, as allegedly indefinite respectfully is traversed. The Office Action indicates that the claims are indefinite for using "about" to define the number of amino acids represented by X_1, X_2, X_3 or X_4.

Applicants maintain that claims 2 and 5 are clear as written. Nevertheless, in order to further prosecution, claims 2 and 5 have been canceled herein in favor of new claims 14, 21, 24 and 25, which do not recite the word "about." In view of the claim cancellations, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be removed.

Regarding the rejection of claims 1 to 4 under 35 U.S.C. § 102 over Tatemoto et al.

The rejection of claims 1 to 4 under 35 U.S.C. § 102(b) as allegedly anticipated by Tatemoto et al., FEBS Letters 153:248-252 (1983), respectfully is traversed. Tatemoto et al. report a 27-residue peptide, termed a PHI peptide, isolated from porcine brain. The Office Action indicates that this peptide contains the three residue motif "SRL."

Claims 1 to 4 have been canceled herein in favor of new claims 13 to 23. Applicants therefore will address this ground for rejection as it applies to these new claims.

Regarding new claims 13 and 21 to 23

Applicants submit that new claims 13 and 21 to 23, directed to conjugates containing a peptide that selectively homes to brain linked to moiety that is a toxin, drug, chemotherapeutic agent, cell or liposome, are novel over the cited reference. Tatemoto et al. describe the sequence of a PHI peptide that can be isolated from brain and intestine (see abstract and figure 4) but do not teach the claimed conjugates in which a brain homing peptide is linked to a toxin, drug, chemotherapeutic agent, cell or liposome. In view of the above, Applicants submit that Tatemoto et al. cannot anticipate the invention of claims 13 and 21 to 23.

Regarding claims 14 to 20

New claim 14 is directed to a peptide that selectively homes to brain and has the amino acid sequence X_1SRLX_2 (SEQ ID NO: 45), where X_1 and X_2 each is 1 to 10 independently selected amino acids. New claims 15 to 20 depend from claim 14 and, thus, include all limitations of the base claim. From the definitions of X_1 and X_2, it can be seen that the maximum length of the claimed X_1SRLX_2 (SEQ ID NO: 45) peptide is 23 residues. In contrast to the claimed invention, Tatemoto et al. describe the PHI peptide, which has a length of 27 amino acids (see page 251, figure 4). Thus, Tatemoto et al. cannot anticipate the peptides of claims 14 to 20, which have a length of at most 23 amino acids.

Regarding the rejection of claims 1 and 5 to 8 under 35 U.S.C. § 102(b) over Beinfeld

The rejection of claims 1 and 5 to 8 under 35 U.S.C. § 102(b) as allegedly anticipated by Beinfeld, Biochem. Biophys. Res. Comm. 127:720-725 (1985), respectfully is traversed. The Office Action indicates that Beinfeld describes CCK peptides with the motif "VLR" that home to brain as evidenced by their greater abundance in brain than intestine (Beinfeld at page 720, line 2).

Claims 1 and 5 to 8 have been canceled herein in favor of new claims 13 and 24 to 41. Applicants therefore will address this ground for rejection as it applies to these new claims.

The X_3VLRX_4 (SEQ ID NO: 46) compositions of the invention relate to peptides that selectively home to brain. For example, when phage displaying such peptides are administered to mice via tail vein injection, they accumulate in brain (see page 33, lines 20-28, and Table 1) and are isolated from brain in preference to kidney (page 37, lines 1-9). In contrast, Beinfeld does not show that any form of CCK peptide containing the "VLR" motif homes to brain. Rather, Beinfeld merely reports that CCK can be isolated from brain, and that some form of CCK might have a physiological role in brain. The mere isolation of CCK from brain can be a function, for example, of the selective expression of a CCK peptide or precursor in brain and is not evidence of "selective homing." In view of the above, Beinfeld has not demonstrated that their CCK peptides have the selective brain homing activity which characterizes the peptides of the present invention.

Further Regarding claims 13 and 25 to 27

Applicants submit that Beinfeld does not anticipate the invention of claims 13 or 25 to 27, which are directed to conjugates containing a peptide that selectively homes to brain linked to a toxin, drug, chemotherapeutic agent, cell or liposome. The specification teaches conjugates in which an organ homing molecule is linked, for example, to a toxin such as ricin or to a drug for the purpose of directing homing of the moiety to brain, and that such conjugates are useful, for example, in reducing undesirable side effects that can result from non-specific drug delivery (page 1, line 26, to page 2, line 5). In contrast, Beinfeld does not teach conjugates in which a peptide that selectively homes to brain is linked to a toxin, drug, chemotherapeutic agent, cell or liposome. At most, the cited reference by Beinfeld reports the use of peptide "L-8-D" (leu-arg-ala-val-leu-arg-pro-asp) in preparing antibodies and the conjugation of L-8-D to bovine serum albumin (page 721, first paragraph of Methods). Beinfeld also reports that peptide Y-9-D (the L-8-D peptide with an amino terminal tyrosine) can be ^{125}I-labeled for use in an in vitro radioimmunoassay (page 721, second paragraph of Methods). However, Beinfeld does not teach the claimed conjugates in which a brain homing peptide is linked to a toxin, drug, chemotherapeutic agent, cell or liposome and, therefore, cannot anticipate the invention.

Further Regarding new claim 24

Applicants submit that new claim 24 also is novel over Beinfeld. Claim 24 is directed to a cyclic peptide that

selectively homes to brain and which has the amino acid sequence X_3VLRX_4 (SEQ ID NO: 46), where X_3 is 0 to 10 independently selected amino acids and X_4 is 1 to 20 independently selected amino acids. In view of the definition of X_3 and X_4, the cyclic peptide of claim 24 is at most 33 residues in length. Beinfeld does not teach the claimed cyclic brain homing peptide which has at most 33 residues, but at best, reports pre-pro-CCK, a 113 residue polypeptide having three cysteine residues. In view of the above, Applicants submit that new claim 24 is novel over the cited reference.

Regarding claims 28 to 41

Applicants submit that new claims 28 to 41 also are novel over Beinfeld. Claims 28 to 41 are directed to peptides that selectively home to brain and contain the sequence CVLRGGRC (SEQ ID NO: 4), WRCVLREGPAGGCAWFNRHRL (SEQ ID NO: 16), CENWWGDVC (SEQ ID NO:2), CGVRLGC (SEQ ID NO:6), CKDWGRIC (SEQ ID NO:7), CLDWGRIC (SEQ ID NO:8) or CTRITESC (SEQ ID NO:9). Although Beinfeld describes CCK sequences shown in figure 1 (page 721), this reference does not teach sequences SEQ ID NOs:2, 4, 6, 7, 8, 9 or 16. Thus, claims 28 to 41 are novel over Beinfeld.

III. CONCLUSION

In view of the amendments and remarks submitted herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to that effect. The Examiner

is invited to call the undersigned agent or Cathryn Campbell if there are any questions relating to the subject application.

Respectfully submitted,

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Date

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